LARA Quarterly Progress Report: 1/16/2023-04/15/2023
2022 Veteran Marijuana Research Grant

Investigating the Therapeutic Impact of Cannabinoids on Neuroinflammation and Neurobiological Underpinnings of Suicide Ideation in Veterans with PTSD

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Project Aims:

This study, referred to here as the 'Neuroimaging Study,' is a supplement (add-on) to our ongoing VMR study (Wayne State Warriors Marijuana Clinical Research Program: Investigating the Impact of Cannabinoids on Veterans' Behavioral Health", PIs: Lundahl and Ledgerwood), which will be referred to as the 'Parent Study'. **The Neuroimaging Study will be the first-ever neuroimaging study of cannabis treatment in US armed forces veterans with PTSD, or in any population.** The Parent Study involves randomizing 200 Michigan veterans with PTSD into one of four different THC (∆9-tetrahydrocannabinol) : CBD (cannabidiol) dose conditions (High THC:High CBD; HighTHC:Low CBD; Low THC:High CBD, and Low THC:Low CBD) for a 12-week treatment phase. For this Neuroimaging Study, half of the 200 participants from the Parent Study (N=100; 25 of the 50 participants in each dose condition) will additionally complete two brain imaging assessments: one before (i.e., 'baseline' scan) and one after the 12-week treatment period (i.e., 'post-treatment' scan). **Primary outcomes include:** A) neuroinflammatory state as measured via positron emission tomography (PET) imaging with the radiotracer, α-[^{11}C]methyl-L-tryptophan (AMT); B) resting or 'basal' neural network communication as measured via functional magnetic resonance imaging (fMRI); and C) brain activation during well-validated inhibitory control (Go/No-Go) and emotion regulation (Emotional Stroop) tasks as measured via fMRI. We will focus on brain regions that are consistently linked to both PTSD symptom severity and suicidal ideation, and that are densely populated with cannabinoid receptors (which are modulated by acute cannabis/cannabinoid administration). Further, the collection of whole-brain, multi-modal neuroimaging data (structural MRI, functional MRI, and PET imaging data) during the same session will allow us to explore the impact of cannabis/cannabinoid administration on the relationship between neuroinflammatory state and neural network activation and interactions throughout the brain, and link these brain metrics to clinical outcomes (e.g., reduction in suicidal ideation or PTSD/depression symptoms over time). This highly innovative approach will provide unprecedented insight into the neurobiological underpinnings of PTSD and suicidal ideation and the potential therapeutic effects of cannabis (and associated brain mechanisms) on these and other critical outcomes (e.g., quality of life, depressive symptoms). Findings from this Neuroimaging Study may also identify veterans who will benefit most from cannabinoid therapeutics and specific THC:CBD dose combinations therein, and thus, may inform a personalized medicine approach for veterans with PTSD in the future.

1. Project Milestones

• Percent (%) completion of the project objectives

Preparation for Neuroimaging Study Launch: 70%
Neuroimaging Study Progress: 0%
Neuroimaging Study Analyses/Findings Communication: 0%

• Project Progress – Brief outline of the work accomplished during the reporting period and the work to be completed during the subsequent reporting period(s).

Since January 2023, we have continued to refine our protocols and procedures to prepare for study launch. In particular, we developed the in-scanner cognitive paradigms to evaluate inhibitory control proficiency, emotional interference of executive function, and reward processing in our research subjects. We tested the full MRI protocol on a phantom and on one human subject, and are currently optimizing the sequences and cognitive tasks. This includes developing our quality control, redundant backup, and data processing pipeline and procedures for neuroimaging, behavioral, and physiology data that will be collected for this study on our secure departmental server in the Tolan Park Medical Building. Our computer scientist/research technician is developing data management procedures and data analysis pipeline that are scripted using computer code (python and unix). Notably, this data analysis pipeline leverages our multi-echo BOLD fMRI sequence to de-noise brain images and maximize rigor and reproducibility. This code will be maintained in a central secure location to ensure repeatability of analysis from raw data to all results. During the next reporting period, we will perform another test MRI scan, if needed, and submit the full MR protocol to the MRI Research Committee for review.

Since the last progress report, we installed two high-sensitivity pass-by ferromagnetic metal detectors (Ferroguard Screener®) that will be used to screen potential participants for safety for MRI scanning. One detector is mounted in our laboratory and the other at the MRI center. We are now working with the MR Research Facility to test and refine a universal MRI safety screening protocol for use in all MRI studies conducted at the Facility, including this study. These procedures will be added to the screening visit for the Parent study, to screen potential participants for the supplemental Neuroimaging Study. Once complete, we will have a 2-visit (screening and scan day visits), 5-step screening process to ensure subject safety for MRI scanning. Additionally, we received and installed an ultra-low temperature freezer (-80C) for biological specimen storage and a centrifuge for sample processing. We are awaiting delivery for a backup CO_2 device for the freezer, which will maintain freezer temperature in the event of a power outage.

Of note, both the MRI and PET imaging centers have purchased new scanners that will be installed in Fall/Winter 2023/2024. At the MRI center, Dr. Haacke received an an NIH High-End Instrumentation grant (Haacke, S10OD028724, May 2022) to support the purchase of a state-of-the-art Siemens MAGNETOM Cima.X 3 Tesla research scanner. The Cima.X is a whole-body superconductive Zero Helium Boil-Off 3T magnet and is

the latest upgrade for the MAGNETOM Prisma system. The Cima.X will include the 3T PowerPack for exploration, Gemini gradients, 64-channel head/neck coil, and streamlined software packages for cutting-edge neuroimaging research. Separately, Karmanos Cancer Institute (KCI), who owns the WSU PET center, purchased a new PET camera that will replace the existing GE Discovery PET/CT system. The state-of-the-art Siemens Vision 600 PET/CT system has been ordered and delivery is anticipated in Fall 2023. This is the latest generation of PET/CT scanners, combining a PET detector ring of lutetium oxyorthosilicate (LSO) crystals with a high-end 64-slice CT system to yield an 82-cm-diameter detector ring with an axial field-of-view of 26.3 cm. Notably, system sensitivity is excellent (16 cps/kBq) and the detector time resolution is 214 picoseconds which will yield 3.7mm isotropic spatial resolution. Prior to installation, the PET scanning protocol will be submitted to the PET Center's Radioactive Drug Research Committee (RDRC) for review/approval. Once approved, the study protocol will be added to WSU's existing FDA IND for this radiopharmaceutical (i.e., PET tracer) and submitted for FDA review.

We have continued to coordinate closely with the Parent Study team, including regular meetings and coordinating the protocol and IRB submissions. We have also continued to refine our internal protocols and develop and test the behavioral tasks and questionnaire measures that will be used during the brain imaging visits. A full run-through of the non-MRI and non-PET related laboratory procedures and staff training is planned in May 2023. Once complete, study procedures and protocols will be finalized and approved by the MR Research Facility and PET Center RDRC, we will be ready to begin enrollment once the Parent Study commences.

• Noteworthy Accomplishments – Identify and describe any milestones reached or noteworthy accomplishments completed during the period.

N/A – The study is in the Study Preparation phase.

2. Delays – Brief description of problems or delays, real or anticipated, which should be brought to the attention of the Grant Administrator.

None.

3. Statement concerning any significant deviation from previously agreed-upon Statement of Work.

None.

• Attachments and Other Materials – Provide project materials developed and implemented during the reporting period (e.g. newspaper articles, newspaper advertisements, forms, brochures, announcements, studies, reports, analyses, audits, etc.)."

Please see attached for WSU's Granting Policies for Charging Personnel Effort.

4. **Financial expenditures of grant money and other contributions to the project, in-kind and/or direct funding.**

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CATEGORY	TOTAL BUDGET	EXPENSES (through 4/4/2023)	% of Budget Spent
Personnel/Fringe	$2,182,687.00	$73,616.60	
Equipment	$42,000.00	$36,143.00	
Supplies/Other	$966,334.00	$1,846.56	
Computers	$12,000.00	$4,581.00	
Consultants	$12,000.00	-	
Travel	-	-	
DIRECT TOTALS	**$3,215,021.00**	**$116,187.16**	
Indirect Costs- 10%	$321,502.00	$11,618.72	
BUDGET TOTALS	**$3,536,523.00**	**$127,805.88**	**3.61%**

Respectfully submitted,

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April 15, 2023